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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,803	02/05/2001	Vanitha Ramakrishnan	MP198-149P1USRCE2M	3916

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Intellectual Property Group
MILLENNIUM PHARMACEUTICALS, INC.
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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/775,803	RAMAKRISHNAN ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,8,10,13,15,21,23,24,26,27,28,29,30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,8,10,13,15,21,23,24,26,27,28,29,30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Non-Final Rejection

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/1/04 has been entered.

Claims 1, 3, 5, 8, 10, 13, 15, 21, 23, 24, and 26-30 are pending.

Applicants' amendment filed on 4/1/04 is acknowledged.

Specification

A SEQ ID NO: for the nucleotide sequences listed in Figures 1-4 are missing. In view of the CRF, the SEQ ID NOs: are in the CRF. The specification is objected under 37 CFR 1.821(d) for non-sequence compliance, suggest amending the specification on pages 3-4 with the proper SEQ ID NOs.

The disclosure is objected to because of the following informalities: the status (e.g., pending, abandoned, patented US Patent No.) of US applications listed on page 18, line 1 is missing.

Appropriate correction is required.

Claim Objections

Claims 5 and 10 are objected to because of the following informalities: a nucleic acid molecule does not "encode" a modified GP V gene although they may comprise a modified GP V gene. Appropriate correction is required.

Claims 8 and 13 are objected to because they depend from claims 5 and 10, respectively.

Claim 24 is objected to because of the following informalities: the phrase "wherein said transgene **has** been introduced into said mouse or an ancestor of said mouse" is grammatically incorrect. Suggest replacing "has" with -- had --. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5, 8, 10, 13, 15, 21, 23, 24, and 26-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a transgenic mouse whose genome comprises a homozygous disruption in its endogenous GPV gene and wherein the transgenic mouse has a decreased bleeding time compared to a wild type mouse, comprising the steps of: (a) producing a construct comprising a nucleic acid molecule encoding a modified murine GP V, wherein the nucleotides encoding Met 1 to Leu 389 of SEQ ID NO: 12 were replaced by a selectable marker; (b) introducing the construct into mouse embryonic stem cells, wherein the

introduction of the construct results in a disruption in the GP V gene; (c) introducing the embryonic stem cells into a blastocyst of a mouse; (d) introducing the blastocyst into a pseudopregnant mouse; (e) allowing the blastocyst to develop into a chimeric mouse whose genome comprises a disruption in its endogenous GPV gene; (f) breeding the chimeric mouse to produce a transgenic mouse comprising a heterozygous disruption in the GP V gene; and (g) breeding the transgenic mouse of step (f) to obtain a mouse whose genome comprises a homozygous disruption in its endogenous GPV gene, does not reasonably provide enablement for a transgenic mouse comprising a modified GPV gene, wherein at least one allele of said gene has been modified by a construct which removes a sequence of GP V comprising nucleotides encoding Met1 to Leu 389 of SEQ ID NO: 12 and wherein said mouse has a decreased bleeding time compared to a mouse homozygous for the wild type GP V gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention is directed to making and using a transgenic mouse comprising a modified GP V gene, wherein at least one allele of said gene has been modified by a construct which removes a sequence of GP V comprising nucleotides encoding Met 1 to Leu 389 of SEQ ID NO: 12 and wherein said mouse has a decreased

bleeding time compared to a mouse homozygous for the wild type GP V gene. The invention lies in the field of transgenics.

The specification provides prior art pertaining to the preparation of transgenic mice that were well known in the art (pages 5-13). For example, a transgene can be introduced into the germline of a transgenic mouse by microinjection for production of a transgenic mouse. The art of record teaches a GPV-deficient mouse whose platelets have undiminished thrombin responsiveness and does not exhibit a Bernard-Soulier phenotype (Kahn et al., page 4112, cited on a previous PTO-892). Kahn produced GPV-deficient mice using gene targeting, wherein the entire GPV gene was knockout. The mice responded normally to thrombin and the tail-bleeding times of wild type and GPV deficient mice were indistinguishable (pages 4114-4115). The platelets from GPV-deficient mice responded to 1nmol/L thrombin like wild type mouse (page 4115). In addition, the art of record for GP V teaches that the role of GP V is poorly defined (IDS, Dong, pages 4355 and 4362). Therefore, the state of the art, at the time the application was filed, for transgenics is such that one of skill in the art would be able to produce transgenic mouse comprising a modified gene (e.g. GPV gene), but it is not predictable if the modified gene would result in a particular phenotype.

The specification recites that the invention features a genus of transgenic mice comprising either a non-functional GPV gene or a modified GPV gene and goes on to contemplate that there are techniques for producing the transgenic mice (pages 5-13). The applicants teach a method of generating a transgenic mouse using: 1) The DNA sequence encoding murine GPV wherein the coding region of mouse GPV (including the putative initiator Met to Leu^{389}) was replaced by a neo cassette and injected the vector

into an ES cell line (pages 14-15). The neo clones were identified by positive selection and the clones were injected into embryos from C57BL/6J mice (page 15). Furthermore, the applicants provide characterization of the effect of GPV gene deletion on thrombin-induced platelet function at low concentrations of thrombin (Example 5, pages 22-23). Furthermore, in example 6, the applicants teach that GP V-/- mice have a decrease bleeding time in vivo compared to +/+ mice and +/- GPV mice (pages 23-24). The applicants contemplate that the transgenic mice can be used in a method for identifying agents that modulate a biological response (e.g. thrombotic or pro-thrombotic) (page 25).

In view of the In Re Wands Factors, the specification provides sufficient guidance for one skilled in the art to practice a method of making a transgenic mouse as set forth in the scope of enablement and does not provide sufficient guidance and/or factual evidence for practicing the full scope of the claimed invention. The applicants teach removing the initiator methionine through the signal sequence to leucine 389 of GP V. Kahn teaches removing the entire coding sequence from GP V. The limitation "construct which removes a sequence of GP V **comprising** nucleotides encoding Met 1 to Leu 389 of SEQ ID NO: 12" in the claims reads on the transgenic mouse produced by Kahn. Both methods resulted in non-expression of the GP V gene in GP V -/- mice. Neither the applicants nor Kahn teach measuring the expression of GP V in GP V +/- mice. The applicants teach that the GP V-/- mice have a decrease bleeding time in vivo compared to +/+ mice and +/- GP V mice. In addition, the bleeding time in the +/- mice was not statistically different from either wt or -/- mice. The art of record teaches that GPV +/- and GPV -/- mouse do not have a decrease in bleeding time compared to a wild type mouse (Kahn et al., supra). The conflicting phenotypes display that the art of

transgenics is not predictable art with respect to modifying a gene in a mouse and reasonably predicting the resulting phenotype from the modification. As stated above, the applicants teach that GP V -/- mice had a statistically shorter bleeding time than wt littermates, however, the bleeding time in the +/- mice was not statistically different from either wt or -/- mice. One skilled in the art could use the GP V -/- mice because of the statistically different decreased bleeding compared to +/+ mice, however, the specification does not teach one skilled in the art how to use a mouse with a heterozygous disruption in the GP V gene, wherein the mouse has a decreased bleeding time compared to a wild type mouse because the applicants admit that the bleeding time is not statistically different from either wt or -/- mice. One skilled in the art would not have been enabled to use a transgenic mouse as set forth in the claimed invention without an undue amount of experimentation because the specification does not teach one skilled how to use GP V +/- mouse taught by the specification in any method because the phenotype (bleeding time) of the GP V +/- mice cannot be distinguished from either wt or -/- mice. Thus, one skilled in the art could not rely on the specification for guidance for making and using the transgenic GP V +/- mouse because neither applicants nor the prior art provide a correlation or nexus between the results obtained in the specification with results which the skilled artisan (e.g., Kahn) would reasonably expect to see when producing transgenic GP V +/- mice.

In conclusion, in view of In Re Wands Factors, the claimed invention is only enabled for a method of producing a transgenic mouse whose genome comprises a homozygous disruption in its endogenous GPV gene and wherein the transgenic mouse has a decreased bleeding time compared to a wild type mouse, comprising the steps of:

(a) producing a construct comprising a nucleic acid molecule encoding a modified murine GP V, wherein the nucleotides encoding Met 1 to Leu 389 of SEQ ID NO: 12 were replaced by a selectable marker; (b) introducing the construct into mouse embryonic stem cells, wherein the introduction of the construct results in a disruption in the GP V gene; (c) introducing the embryonic stem cells into a blastocyst of a mouse; (d) introducing the blastocyst into a pseudopregnant mouse; (e) allowing the blastocyst to develop into a chimeric mouse whose genome comprises a disruption in its endogenous GPV gene; (f) breeding the chimeric mouse to produce a transgenic mouse comprising a heterozygous disruption in the GP V gene; and (g) breeding the transgenic mouse of step (f) to obtain a mouse whose genome comprises a homozygous disruption in its endogenous GPV gene, and not enabled for the full scope of the claimed invention. In view of the unpredictability in the art of record for predicting a phenotype in a transgenic mouse with a modified endogenous gene, the lack of guidance in the specification for making and using the claimed transgenic mouse, it would require an undue amount of experimentation for one skilled in the art to make and/or use the full scope of the claimed invention.

Applicants' arguments filed 4/1/04 have been fully considered but they are not persuasive because in view of the In Re Wands Factors the full scope of the claimed invention is not considered enabled. In addition, the amendment to claims 1, 5, 10, 15, 21, 23, 28-30 and claims dependent therefrom still read on the transgenic mouse produced by Kahn. The limitation "construct which removes a sequence of GP V **comprising** nucleotides encoding Met 1 to Leu 389 of SEQ ID NO: 12" embraces the construct taught by Kahn.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 3, 5, 8, 10, 13, 15, 21, 23, 24, and 26-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 3, 5, 8, 10, 13, 15, 21, 23, 24, and 26-30 are rejected under 112 second paragraph because of the term "decreased bleeding time compared to a mouse homozygous for the wild type GP V gene" in the claims is a relative term, which renders the claim indefinite. The term "decreased bleeding time compared to a mouse homozygous for the wild type GP V gene" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. On page 24 of the specification, the applicants teach that GP V -/- mice had a statistically shorter bleeding time than wt littermates, however, the bleeding time in the +/- mice was not statistically different from either wt or -/- mice. Since the claims read on heterozygous GPV mice, the claims do not define what amount of time is considered a shorter bleeding time compared to a mouse with a wild type GPV gene.

Claims 5 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: active steps required for

determining that the bleeding time of the transgenic mouse is less than the bleeding time of a mouse homozygous for the GPV gene. The claim does not define the active steps if the bleeding time of the transgenic mouse is not less than the bleeding time of a mouse homozygous for the GPV gene.

Claims 5, 8, 10, 13 are indefinite because the term "a construct which removes a sequence of GPV comprising nucleotides encoding Met 1 to Leu 389 of SEQ ID NO: 1" in the preamble does not give weight to the production of a transgenic mouse with the claimed phenotype. The body of the claims does not fully and intrinsically set forth all of the limitations of the claimed invention because the steps in the body of the claims do not require the construct used in the pre-amble. The nature of the modified gene in the body of the claim is not defined by the claim.

Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: what type of chimeric mouse or a heterozygous mouse is used in the step (f), e.g., a chimeric mouse with a modified GP V, a chimeric mouse with a modified Factor VIII.

Claims 24 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationship is: how a transgene

comprising a modified GPV gene is introduced into an ancestor of said mouse, when the ancestor of said mouse already expresses a modified GPV protein.

Claims 26 and 27 recite the limitation "The line of claim" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, SPE - Art Unit 1635, can be reached at (571) 272-0760.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

Brian Whiteman
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